REMARKS

Reconsideration and allowance of the subject application are respectfully requested.

Claims 1, 2, 9, 11-13 and 15-35 are pending in the application.

Claims 2 and 22 have been amended to clarify that when the matrix material comprises cellulose, then the matrix material is present in the formulation in an amount of 70-98% by weight. Claims 4-8 have been deleted and the subject matter thereof recited in new claims 31-35, respectively. No claims have been amended to overcome prior art or to alter the breadth of the claims in any manner.

In the July 5, 2001 Office Action, the Examiner rejected the claims over prior art. Applicant submits that the claimed invention is not anticipated or obvious over the cited prior art for the many reasons provided in Applicant's December 4, 2001 Response and for the following reasons.

On page 2 of that Office Action, the Examiner stated that "adequate evidence must be provided to prove dissimilarities between cited art and claimed invention." Based on this requirement raised by the Examiner, Applicant went to great expense and hired an independent professor, Dr. Alfred Fahr, who specializes in pharmaceutical sustems, to conduct experimental tests comparing the claimed invention to the cited prior art. Dr. Fahr conducted the experimental tests and confirmed that the claimed invention is unexpected and has a structure very different from the teachings of the prior art. See the attached Rule 132 Declaration of Dr. Fahr.

In regards to McClelland, see page 4 of the Declaration, in which Dr. Fahr proved that the particle structure in McClelland is very different than the claimed particle structure.

On pages 4-6 of the Declaration, Dr. Fahr discusses the many significant differences between the claimed invention and each of Lang, Norling, Sparks and Motta.

Based on the experimental evidence conducted by Dr. Fahr, and his significant experience in the field pharmaceutical systems, he concludes that the claimed particles are "clearly different from the systems described by McClelland, Lang, Norling, Sparks and Motta." [See page 6, Expertise Section of Rule 132 Declaration.]

For these reasons, the claimed invention is not anticipated, taught or suggested by the cited prior art. Accordingly, Applicant requests that all prior art rejections of record be withdrawn.

In view of all of the objections and rejections of record having been addressed, it is believed that the present application is in condition for allowance and Notice to that effect is respectfully requested.

Respectfully submitted,
Manelli Denison & Selter, PLLC

Jeffrey S. Melcher
Reg. No. 35,950
Tel: 202.261.1000
Fax: 202.887.0336

Customer No. 20736

Prof. Alfred Fahr

Marburg, 19 December 2001

Expertise

about the structure of the product described in US patent application 09/319,541 and differences to various states of art

The invention describes matrix-excipient compounds for the production of controlled release tablets.

Background of the invention: For the prolonged release tablets having a polymer content above 15%, in general a costly granulation process is necessary. Therefore an invention allowing direct compression using a powder mixture would have commercial benefits, it would provide a solution for this commercially very interesting problem.

The applicants provide as a solution free flowing particles (so called compound) characterized by having **simultaneously** the properties:
a) being composed of a non-homogenous matrix material (polymer or lipid), i.e. the phase is discontinuous
b) and composed of an excipient (e.g. lactose) being the continuous phase
c) being particulate, spherical shape
d) having good flow properties and
e) allowing to produce a prolonged release unit by direct compression.

First question arising from the patent application: The structure according to a) to c) was described in schematic drawings, no proof was added which lead to the question by the examiner to provide evidence for this.

The points b) and c) are documented in the patent application by the data in the examples showing direct compression of compounds to tablets with prolonged release

The **second question** arising was, to assess whether the products claimed Muller are different to existing products. Products claimed are:
1. particle compounds for direct compression
2. larger matrix units (e.g. tablets) made from the particle compounds by direct compression.

The task of is this expertise is to provide definite answers to these 2 questions raised.

Regarding the first question, two aspects need to be discussed:
1st analysis: is the claimed structure a) possibly in theory and b) likely to occur?
2nd analysis: Can this be shown by analysis?

Within the **1st question** it has to be discussed if the claimed structure is theoretically possible.

The compound is physically a dispersion, a dispersion being characterized that one phase (discontinuous phase) is dispersed in another phase, the latter being continuous. To fall under the definition of a dispersion, the aggregate state (solid, liquid) is of no relevance.

Dispersion with a low concentration of discontinuous phase are well known, these are for example low concentrated suspension and O/W emulsions (e.g. 20% Intralipid for parenteral nutrition), but also dispersions of high concentration of discontinuous phase, e.g. pharmaceutical pastes (e.g. with ZnO in olive oil as outer phase) or mayonnaise as 50% to 80% dispersion of liquid lipid (oil) in water. This corresponds to the claimed concentrations of matrix materials polymer or solid lipid in the outer phase of lactose.
Conclusion: the described structures are theoretically possible.

The next question within the first analysis is: How likely is it, that the claimed structures are formed?

In the theory of dispersion formation, it is state of the art, that the distinctly lower concentrated phase will be the dispersed phase when applying a normal preparation method, e.g. admixing the lower concentrated phase in one step by stirring (law of phase volumes). This is especially valid, when adding the lower concentrated phase stepwise.

This can also be demonstrated from daily life when preparing a low fat salad dressing, i.e. dispersing about 20% oil in vinegar – an O/W dispersion will result. The same is the case when dispersing lower concentrations of polymer / lipid as matrix material in excipient (lactose).

How about high concentrated dispersions, looking at mayonnaise, that means 80% oil in water. The example demonstrates, that in principle it is possible to have an 80% dispersed phase of e.g. polymer in an outer phase of e.g. lactose.
Basically the existence of mayonnaise seem to contradict the "phase law" – but only at the first glance! According to the phase law, the oil should form the outer phase. But the validity of the phase law is limited by "the law of preparation method". This says, that the type of phase (discontinuous or continuous) depends also on the preparation method. If a special type of preparation method is applied, even the high concentrated phase (i.e. oil in the emulsion and polymer in the compound) can be the dispersed phase.
In case of mayonnaise, the special method of preparation is adding the oil (discontinuous phase) stepwise. One starts with e.g. 20g of water/lecithin phase and adds the oil in 5 g portions. Each time the newly added oil is dispersed in 20 g of water, thus according to the law of phase volumes giving an O/W dispersion, that means the oil is the discontinuous phase.
To summarize: The preparation method needs to consider maintaining and obeying basically the law of phase volumes, i.e. the lower concentrated phase in the actual step of dispersion process will be the inner, discontinuous phase.

In the invention, another preparation method was found also obeying the law of phase volumes:

The particle compounds (= polymer in lactose dispersion) are prepared by an intermediate step of preparing an aqueous dispersion, the second step is spray-drying this dispersion.
Just to give an example:
A polymer-excipient compound should be produced containing as particle 80% polymer as discontinuous phase in 20% lactose as continuous phase (i.e. 80g polymer plus 20g lactose in 100 g particle compound powder).
The aqueous dispersion prepared for the spray-drying process will – according to the invention- e.g. be composed of 80g polymer dispersed in e. g. 200 g of water, 20g lactose dissolved in the water. The lower concentrated compound (polymer) is admixed by a simple stirring process, i.e. adding the polymer as lower concentrated phase (80g) to the higher

volume phase of lactose/water (220g). From this as described above, according to the law of phase volumes the polymer particles will be dispersed as discontinuous phase in the water with lactose.

In the second step, the outer water phase is "shrinked" by removing the water successively by evaporation in the spray-dryer. This shrinking process is continuously leading to a solid particle with still continuous a) concentrated water-lactose phase, with progressing drying b) continuous highly concentrated water lactose phase and finally after complete water removal d) solid continuous lactose phase having just a certain moisture content (e.g. water 3% or so, depending on the spray-drying conditions). This is modeled in Figure 1.
Depending on the concentration of polymer as inner phase, two different surfaces will be obtained:
A. At low polymer concentrations or low evaporation velocity, there is enough lactose to surround the polymer particles as a thick layer, the surface is smooth (Fig. 1d left)
B. At high polymer concentrations or fast evaporation rate, the polymer particles led to slightly embossed structure on the surface (Figure 1d, right).

Conclusion: The described structures are very likely to occur, to be more precise: according to the developed production method, they will form inevitably. From point surprising is the really nice spherical form (cf. comments below) causing the good flow properties.

The next question to be answered is, if this structure as described in the patent application and modeled in Figure 1d) can be shown by electron microscopy.
REM pictures were taken from different compounds.

The spherical character of the particles is proven in Figure 2, a compound composed of 70% ethylcellulose and 30% lactose.

Figure 3 and 4 – compound with only 30% ethylcellulose and lactose:
The surface is rather smooth in excess of lactose leading to a thick coverage with lactose, covering the shapes of the polymer particles
Fig 3 with magnification 3,000 shows the smoothness of the surfaces. This can be seen even more clearly at the magnification of 10,000 (Fig. 4).
Fig. 3 shows also the typical feature of spry-dried particles. Due to the fast water evaporation from the inside, they are hollow spheres, the holes can be seen created by the evaporating water. This was not mentioned in the patent application because it is a general feature of spray-dried particles (please cf. my comments below regarding differences to other patents / patent applications).

Fig. 5 – compound with ethylcellulose 50% and lactose 50%:
The REM picture shows the beginning of a slightly uneven surface attributed to the increasing concentration of the inner phase.

Fig. 6 and 7 – compound of 70% ethylcellulose and 30% lactose:
Fig. 6 shows again the spherical character, and also the hollowness as nicely seen by the particle in the lower middle. Stronger magnification of 10,000 (Fig. 7) reveals the first round shapes on the surface, but still being smooth due to the outside lactose coverage. The ethylcellulose particles (Aquacoat) sprayed in the compound had a diameter of about 200 nm, that means a tenth of the length of the size bar. The maximum size of the elevation in the surface is slightly above 0.2 μm, that means they lactose-covered ethylcellulose particles.

Fig. 8 and Fig. 9 – Aquacoat (ethylcellulose) 30% and lactose 70% compound:
A very fast drying from the surface leads to fast shrinking and the more pronounced exposure of the ethylcellulose particles causing the surface to be uneven. The maximum size of the elevations in the surface is dictinctly above 0.2 µm attributed to a thicker lactose coverage than in Fig. 7.

Fig. 10:
It shows again that the particles as spray-dried product are hollow spheres.

Coming to the **second question** whether the products claimed by Muller are different to existing products. As said above, products claimed are:
1. particle compounds for direct compression
2. larger matrix units (e.g. tablets) made from the particle compounds by direct compression.

WO 94/00111 - McClelland:

McClelland describes a spheronization process, that means particles made by extrusion.
Muller produces the particles by spray-drying.

Based on the different production methods, the resulting particles have a different internal structure.

Particles made by extrusion are solid, not hollow.

Spray-dried particles are in most cases hollow, the REM pictures prove this for the particles described by Muller.

Conclusion 1: The particle structure is different:

In addition, the polymer of the extrusion mass is the constituent to keep together the particle, that means it is the continuous phase (in contrast to Muller where the polymer (or lipid) is the discontinuous phase. This is evident from the fact that when using a too low polymer concentration in extrusion (e.g. Avicel), the pellets will fall apart due to lack of coherent phase.

Conclusion 2: In addition, the polymer phases are in a different state (discontinuous in Muller versus primarily continuous in McClelland).

Thus the products are different.

US Patent 5,006,345 - Lang

Muller describes release from a matrix system, release takes place by the Higuchi law. The matrix system can be compared with a ball of ice cream having pieces of cracknel inside. The pieces of cracknel represent the drug, it diffuses through the ice cream matrix to be released. Release takes place via the Higuchi law.

In contrast to this, Lang is using a membrane surrounding the compressed drug. This can be compared with drug release from a dialysis bag, it releases after the Fick law.

Conclusion: Set up of the systems is different, this is also evident by the different physical laws according to which the release takes place. Systems cannot be identical in structure – even despite made from the same material - when different laws describe the release.

US Patent 5,958,458 – Norling:

The same described for Lang is valid for Norling. Norling also uses membranes (coated cores = membrane around drug core). There is no principle difference between coated tablet and coated pellet, just the size and form of the unit.
It should be pointed out, that systems lead to the same result (i.e. prolonged release), but this does not mean that they are necessarily identical.
To illustrate it from practical life: I can use a mean of transport to go from Washington DC to LA, e.g. a train or a plane. They are both means of transport (in case of the patents "prolonged release units") but nevertheless they are different.

US Patent 5,505,962 - Sparks

Also sparks is using a membrane to control release. It is no matrix as described by Muller.

Conclusions for Norling and Sparks: They are both ,membrane systems, a membrane system is never identical with a matrix system.

US Patent 5,662,935 - Motta

The patent by Motta creates a controlled release tablet by mechanical and electromechanical actions during the compression process.
The principle of Motta is that in the tablet the polymer structure is changed due to special mechanical and electromechanical actions, this is nicely demonstrated in Fig. 5 (before) and Fig. 6 (after). That means the polymers have now according to Motta a special structure to obtain the desired release profile.
There is not this special structure in the invention by Muller = first difference.

Secondly, the invention of Motta targets to accelerate release, Muller wants the opposite. I Fig. 1 after Motta, the release of the tablet produced by the method of Motta is much faster (tablet B) compared to a traditional tablet.
Motta being a release-accelerating system is therefore different to Muller. Systems performing different in release properties cannot be identical.

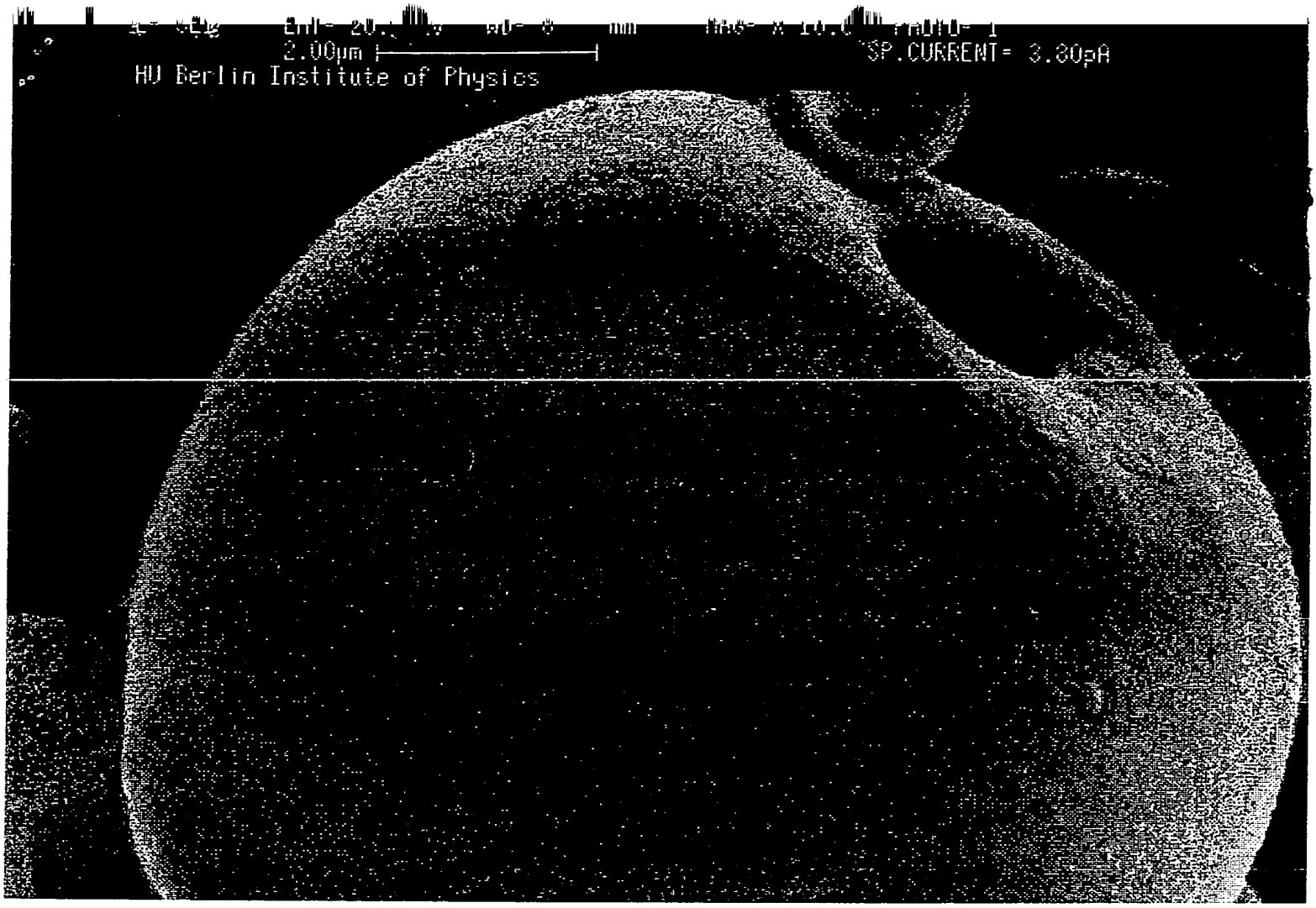
In column 4, line 47 it says that the action is applied up to 20 seconds, that means to compress one single tablet takes up to 20 seconds. Modern machines are compressing 200,000 tablets and more per hour (rotary machines). Assuming a time of 20 seconds for compressing one tablet on a roary machine would mean production of 3 tablets per minute and 180 tablets per hour!! Even assuming only a time of one second per tablet, gives a maximum of 60 x 60 = 3600 tablets per hour. From this, this process is absolutely not economical, the Japanse company Shionogi therefore dropped the development of these tablets.
In contrast, the invention by Muller allows to use normal machine velocity with 200,000 tablets per hour and more. Therefore there is a clear inventive height.

Conclusion: The systems by Muller and Motta are different, clearly proven by the Fig. 5 and 6 showing the change in polymer structure whereas in Muller the original polymer structure remains. Motta is release-accelerating, Muller prolonging.

Overall Conclusions:

The structures described by Muller are
1. theoretical possible
2. likely to occur
3. are proven by REM investigations

The systems described by Muller (particle compounds, release units produced from the compounds) are clearly different from the systems described by McClelland, Lang, Norling, Sparks and Motta.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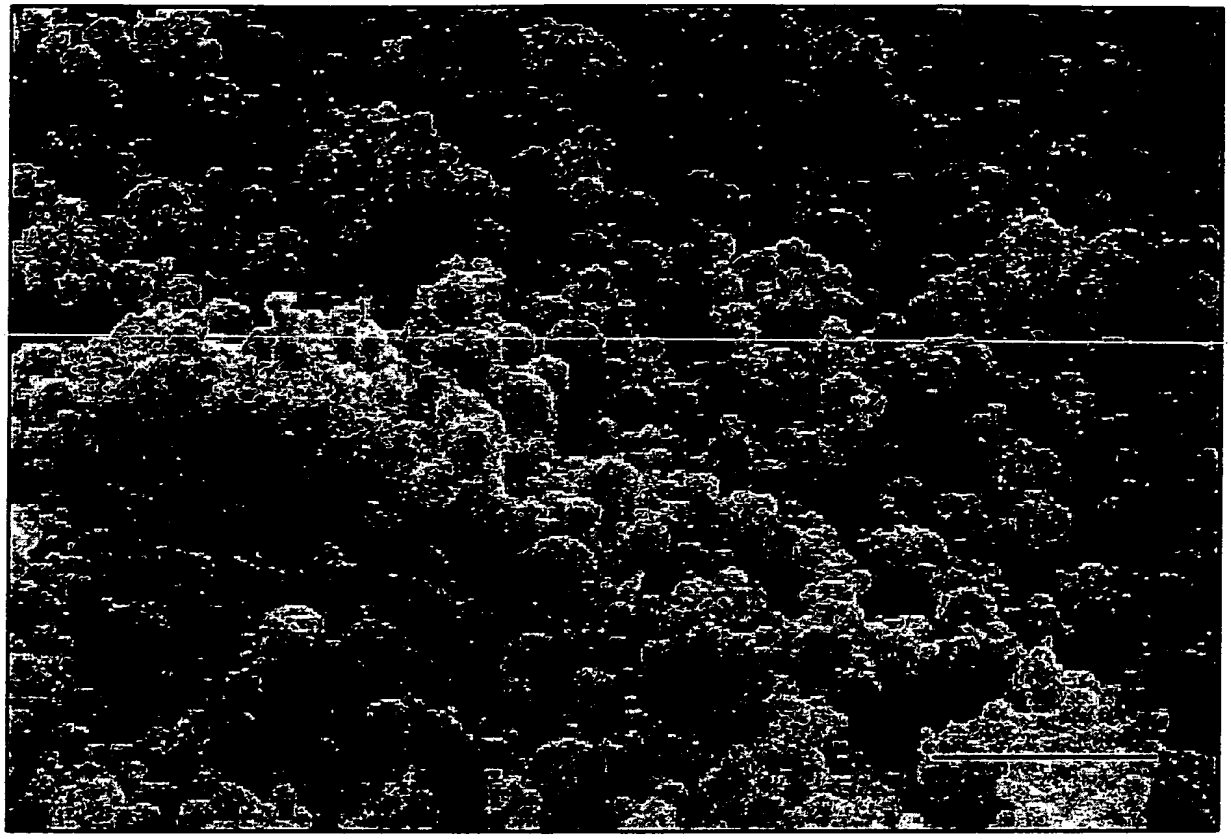

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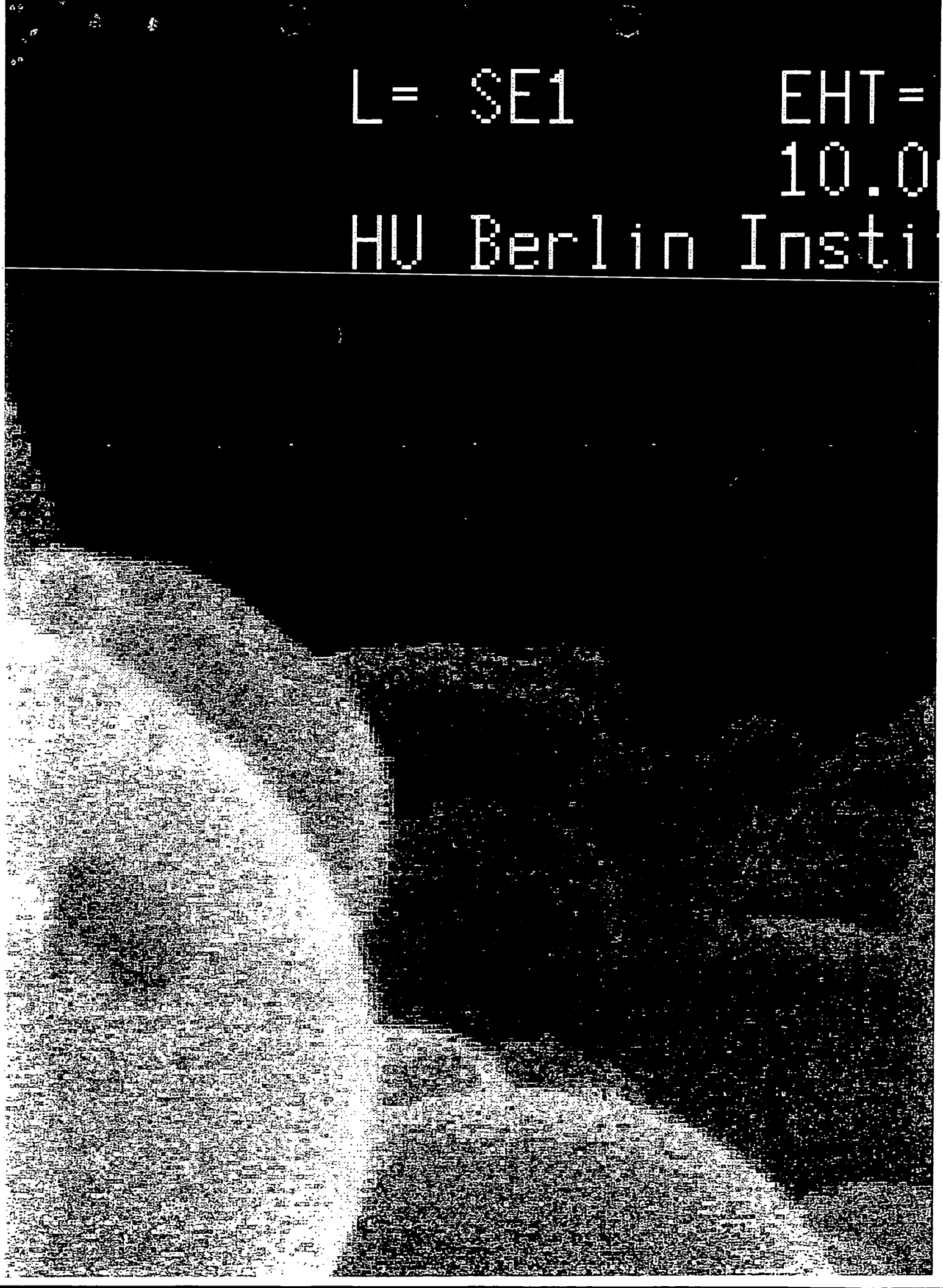
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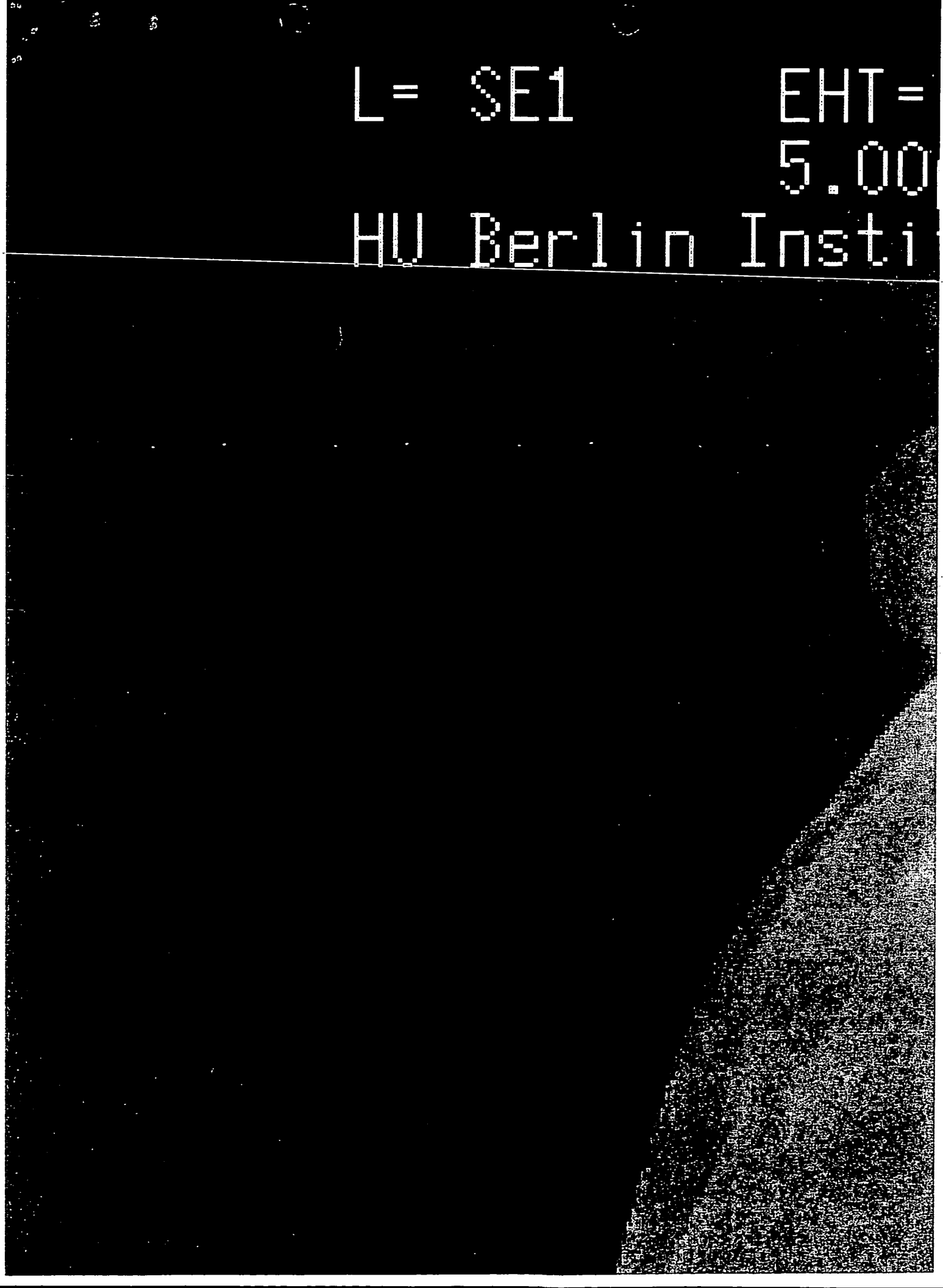
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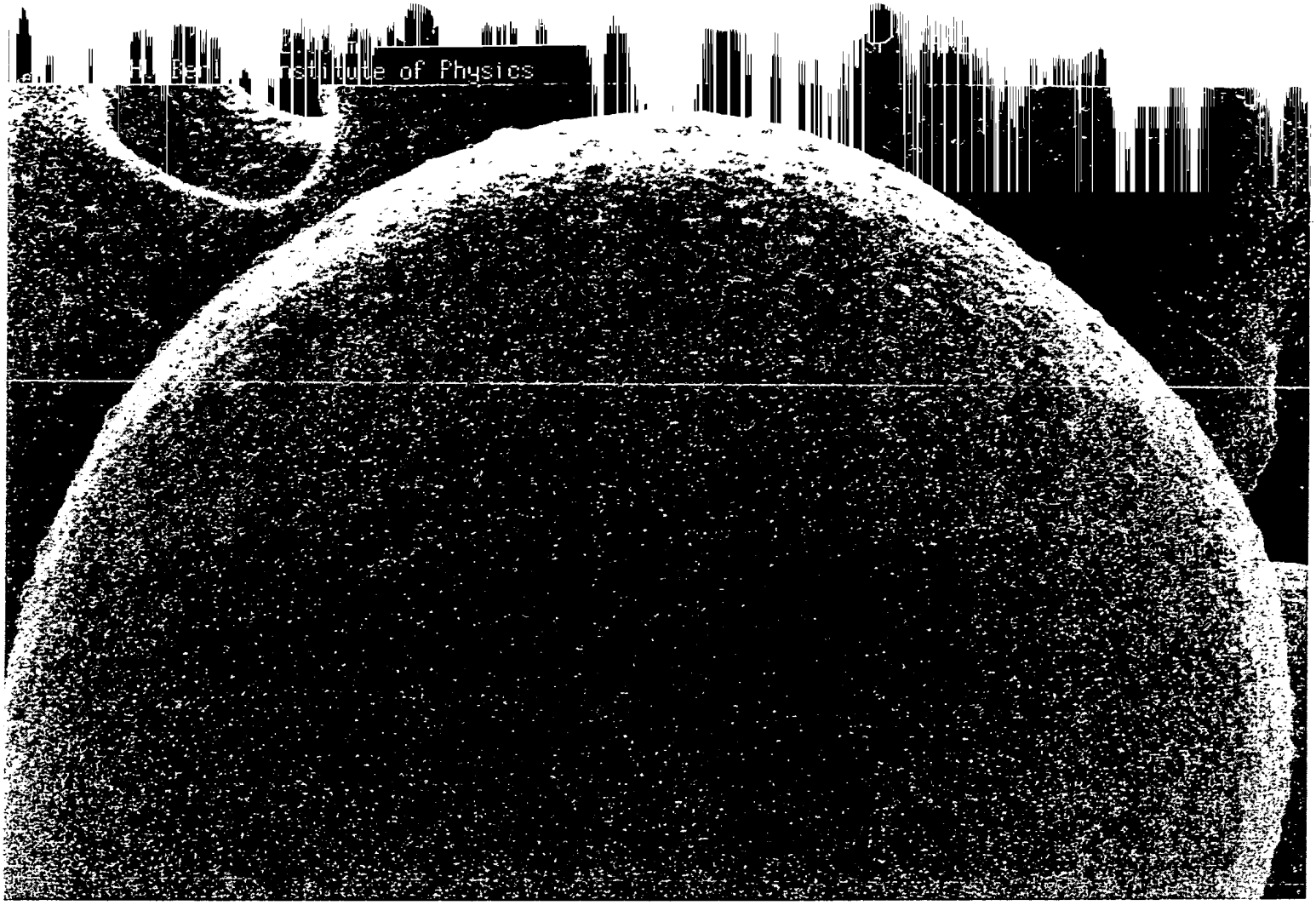
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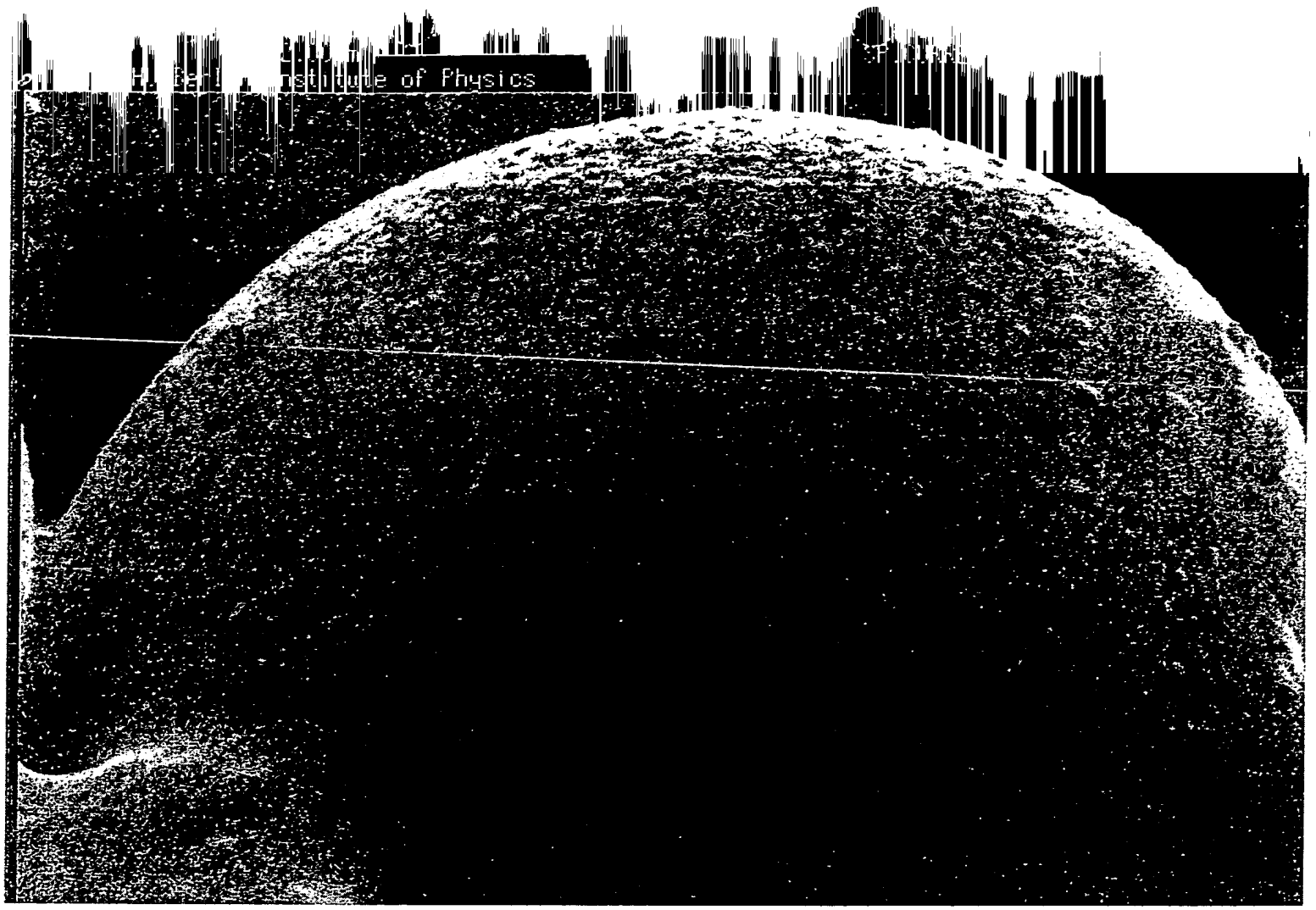
Institute of Physics

Curriculum Vitae

Name	Alfred Fahr
Birth	17. November 1949
Birthplace	Meersburg / Germany
Nationality	German
Languages	German, English French: basic knowledge

Education

Grammar school	1956-1964	Meersburg
Apprenticeship	1964-1967	Electronic Engineer, AEG-Telefunken, Konstanz
High school	1967-1971	Konstanz, Stuttgart
University	1972-1977	Universität Konstanz, subject: Biology and Physics
	1977-1978	Biophysics and Biochemistry, Merton College, University of Oxford, UK
Scholarship		German National scholarship („Studienstiftung des Deutschen Volkes")
PhD	1978-1982	„Photoelectric investigations of bacteriorhodopsin and rhodopsin at artificial lipid membranes: a kinetic analysis"
Associate Professor (Habilitation)	30.12.1994	Pharmaceutical Technology, Pharmaceutical Institute, Universität Basel, Switzerland. Thesis: „Biophysical aspects of liposomal cyclosporin formulations"
Professorship	1.4.1996	Appointment to tenure „Professor für Pharmazeutische Technologie" at Philipps Universität Marburg, Germany

Professional Employment

1978-1982	Research Associate at the Universität Konstanz: Interaction of lipid bilayer membranes and liposomes with membrane proteins (Bacteriorhodopsin, Rhodopsin, Na^+/K^+-ATPase, photosynthetic system)
1981	Invitation by the Academy of Science in Moscow for laboratory work and lectures
1982-1986	Research Asscociate at the Free University of Berlin. Head of a German National research fund-project for patch-clamp-methodology and membrane transport
1986-1996	Research Biophysicist and Pharmacist, Sandoz Pharma Ltd. Basel, Switzerland
since 1996	Tenure professor at Philipps Universität, Marburg, Germany in the institute of Pharmaceutical Technology and Biopharmaceutics

Areas of Work:

Pharmacokinetic studies for bioavailability and metabolism of drugs and excipients. Pharmacodynamics/Pharmacokinetics-modeling.

Studies for investigating correlations between human pharmacokinetics and animal pharmacokinetics. Modeling of drug metabolism.

Non-viral delivery systems for gene therapy

Opsonisation processes during in vivo-application of liposomal formulations

Additional Knowledge

Teaching Experience:
Tutor for physical chemistry and biophysics for biologists und chemists at Konstanz University.
Practical physics and statistics for biologists and medical doctors at Free University of Berlin.
Teaching scientists pharmacokinetics at international pharmaceutical companies
Statistic courses for technicians in Sandoz Pharma Ltd.
Moderation and organisation of seminars in the Institute of Pharmaceutical Technology at Basel University. 91/92: "Liposomes - Production and pharmaceutical applications; 92: "Drug Targeting"
Lecturing since 1993 'Mathematics for Pharmacists'; teaching basic courses in pharmaceutical technology
Tutor for diploma and thesis students
Organisation of an international liposome meeting at Basel University in 1994.
Establishment and supervision of experiments in the practical course „Galenic Pharmacy: liquid and sterile formulations and special carrier systems".
Giving lecture at German Pharmacists Society seminar (APV)

Animal Work:
Rat liver cell cultures, rat liver perfusion, hind limb perfusion of rats, NMR of perfused rat- and rabbit hearts, pharmacokinetics of drugs and carrier-systems in rats, autoradiography

Technical-Scientific Methods in Pharmacy:
Planar bilayer membranes, liposome technology, powder technology, membrane transport, Langmuir-Blodgett-Film, patch-clamp-method, surface analysis, rheology, swelling pressure, dynamic light scattering, fluorescence spectroscopy, pharmacokinetics.

Relevant Experience for the Job Position

Experience in scientific investigation and reporting of:

- membrane biophysics
- membrane biochemistry
- mathematical formulation and kinetic analysis of biological processes
- statistical experimental design and analyses
- manufacturing and characterisation of modern carrier systems with biological models
- testing and characterisation of classical carrier systems

Experience in scientific and technology transfer for industrial applications:

- Interactions of formulations with the target organ
- Optimisation of formulations
- in vitro/in vivo correlations
- Pharmacokinetics
- drug targeting, bionics, gene therapy
- Membership of relevant bodies, e.g. member of the executive committee of APHW EUCOR (education partnership University-Industry EUCOR)

Experience in the interdisciplinary management of scientific investigation:

- Project management in the pharmaceutical industry (coordination of preclinical research, biopharmaceutics, pharmaceutical technology)
- coordination of basic research at universities with industrial potential

Basel, October 2

Dr. Alfred Fahr

List of Publications

1. Bamberg E. & Fahr A.: Photocurrents induced on black lipid membranes by purple membranes: A method of reconstitution and a kinetic study of the photocurrents. Annals New York Academy of Sciences 78, 324-327, 1980.

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